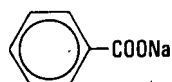


Ucephan™ (10% Sodium Benzoate and 10% Sodium Phenylacetate Oral Solution)

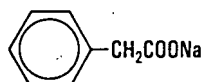
For oral use only. **Not for parenteral use.** Concentrated solution. Must be diluted to appropriate strength prior to administration. (See **Dosage and Administration.**)

Description

Ucephan™ (10% Sodium Benzoate and 10% Sodium Phenylacetate Oral Solution) is a concentrated solution to be diluted and used as an oral adjunctive therapy in patients with urea cycle enzymopathies (UCE). Ucephan is an aqueous solution of 10% sodium benzoate and 10% sodium phenylacetate. The structural formulas of the active ingredients are:



Sodium Benzoate NF



Sodium Phenylacetate

Each 100 mL contains:

Sodium Benzoate NF	10 g
Sodium Phenylacetate	10 g

pH adjusted with Sodium Hydroxide NF

pH: Approx. 6.0

Calculated Osmolarity: Approx. 2620 mOsm/L

Electrolyte (mEq/100 mL): Sodium 130

Ucephan is supplied in multiple-unit amber glass bottles containing 100 mL, with child-resistant tamper-evident bottle caps. The bottle should not be used initially if the breakaway ring is separated.

Clinical Pharmacology

Sodium benzoate and sodium phenylacetate are metabolically active compounds which decrease elevated blood ammonia concentrations in patients with inborn errors of ureagenesis. The mechanisms for this action are conjugation reactions involving acylation of amino acids. In primates, benzoate conjugates with glycine to form hippurate, and phenylacetate conjugates with glutamine to form phenylacetylglutamine. One mole of hippurate contains one mole of nitrogen, and one mole of phenylacetylglutamine contains two moles of nitrogen. Diversion of nitrogen to these conjugation products results in decreased ammonia formation.

The syntheses of hippurate and phenylacetylglutamine occur via two-step pathways requiring adenosine triphosphate and coenzyme A to form the acyl-coenzyme A intermediates and subsequent amino acid-specific transacylation of glycine and glutamine, respectively.

Studies have shown that benzoate and phenylacetate activate these conjugation pathways which then substitute for or supplement the defective ureagenic pathway in patients with urea cycle enzymopathies, and thereby help prevent the accumulation of ammonia. Sodium benzoate and sodium phenylacetate have been used successfully as adjunctive therapy in UCE patients with deficiencies of the following urea cycle enzymes: carbamylphosphate synthetase, ornithine transcarbamylase, and argininosuccinate synthetase. The therapeutic regimens, which also included dietary manipulation and amino acid supplementation, were effective in the long term management of UCE patients. The survival rate in patients with complete enzyme deficiencies was approximately 80% with this combined regimen in what was previously an almost universally fatal disease within the first year of life. The survival rate for each complete enzyme deficiency studied was: carbamylphosphate synthetase - 75%, ornithine transcarbamylase (males) - 59%, argininosuccinate synthetase - 96%. Survival in heterozygous females with partial ornithine transcarbamylase deficiency was 95%, and for patients with other partial deficiencies, 86%. Results of clinical studies indicated that early diagnosis and treatment are important in minimizing developmental disabilities. Reversal of pre-existing neurologic impairment is not likely to occur with treatment and neurologic deterioration may continue in some patients.

Pharmacokinetic studies have not been conducted in the primary patient population (neonates, infants, and children). Preliminary pharmacokinetic data were obtained from only three normal adult subjects and the overall disposition of sodium benzoate, sodium phenylacetate and their metabolites has not been fully characterized. These preliminary pharmacokinetic studies suggest that peak blood levels of benzoate or phenylacetate occur within one hour after a single oral dose of sodium benzoate or sodium phenylacetate, respectively. A majority of the administered compound (approximately 80-100%) was excreted by the kidney within 24 hours as the respective conjugation product, hippurate or phenylacetylglutamine. The major sites for metabolism of benzoate and phenylacetate are the liver and kidney.

Indications and Usage

Ucephan™ (10% Sodium Benzoate and 10% Sodium Phenylacetate Oral Solution) is indicated as adjunctive therapy for the prevention and treatment of hyperammonemia in the chronic management of patients with urea cycle enzymopathies involving partial or complete deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase, or argininosuccinate synthetase.

Contraindications

There are no known contraindications.

Warnings

There have been reports of a possible link between parenteral solutions preserved with benzyl alcohol and morbidity and mortality in low birthweight infants. Use of preserved parenteral solutions was associated with high blood and urine levels of benzyl alcohol and its metabolites, benzoate and hippurate. It is theorized that the immature liver may not be capable of adequately metabolizing these compounds. Therefore, Ucephan should not be administered to low birthweight infants unless, in the opinion of the physician, the benefits outweigh the risks.

Solutions containing sodium ions should be used with great care, if at all, in patients with congestive heart failure, severe renal insufficiency, and in clinical states in which there is sodium retention with edema.

In patients with diminished renal function, administration of solutions containing sodium ions may result in sodium retention.

Precautions

General:

For oral use only. **Not for parenteral use.**

The bottle should not be used initially if the breakaway ring is separated.

Ucephan is a concentrated solution and should be diluted before use (see **Dosage and Administration**).

Ucephan is not intended as sole therapy for UCE patients. It should be combined as adjunctive therapy with dietary management (low protein diet) and amino acid supplementation for optimal results.

Caution should be exercised when administering Ucephan to patients with neonatal hyperbilirubinemia since *in vitro* experiments suggest that benzoate competes for bilirubin binding sites on albumin.

The benefits of Ucephan in treating neonatal hyperammonemic coma have not been established. The treatment of choice in neonatal hyperammonemic coma is hemodialysis. Peritoneal dialysis may be helpful if hemodialysis is not available.

Care should be exercised when administering solutions containing sodium to patients with renal or cardiovascular insufficiency, with or without congestive heart failure, particularly if they are postoperative.

Ucephan should not be administered to patients with known hypersensitivities to sodium benzoate or sodium phenylacetate. No such cases of hypersensitivities have been reported.

Drug Interactions:

Some antibiotics such as penicillin may compete with conjugated products of Ucephan for active secretion by renal tubules which may affect the overall disposition of Ucephan.

Probenecid is known to inhibit the renal transport of many organic compounds including amino hippuric acid and may affect renal excretion of the conjugation products of Ucephan.

There have been reports that valproic acid can induce hyperammonemia. The proposed mechanism is direct inhibition of carbamylphosphate synthetase or interference with the synthesis of its activator, N-acetylglutamate. Therefore, administration of valproic acid to UCE patients may exacerbate their condition and be antagonistic to the efficacy of Ucephan.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Sodium benzoate has been extensively tested as a food preservative and results indicate it is not mutagenic or carcinogenic and has not been found to impair fertility. Carcinogenicity, mutagenicity and fertility studies of sodium phenylacetate have not been conducted.

Usage in Pregnancy:

Pregnancy Category C. Animal reproduction studies have not been conducted with Ucephan. It is also not known whether Ucephan can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Ucephan should be given to a pregnant woman only if clearly needed.

Nursing Mothers:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Ucephan is administered to a nursing woman.

Pediatric Use:

See Dosage and Administration.

Adverse Reactions

Nausea and vomiting have occurred in patients treated with sodium benzoate and sodium phenylacetate, usually during intravenous administration of these compounds.

Due to structural similarities between benzoate and salicylates, Ucephan™ (10% Sodium Benzoate and 10% Sodium Phenylacetate Oral Solution) may have the potential to cause side effects associated with salicylates such as exacerbation of peptic ulcers, mild hyperventilation, and mild respiratory alkalosis.

In view of the sodium content of this product, the possibility of hypernatremia should be considered. Hypernatremia may be associated with edema and exacerbation of congestive heart failure due to retention of water, resulting in an expanded extracellular fluid volume.

If an adverse reaction does occur, discontinue administration, evaluate the patient, and institute appropriate therapeutic countermeasures.

Overdosage

Four adverse experiences have been reported involving overdoses of sodium phenylacetate and/or sodium benzoate in UCE patients. One patient who was inadvertently given a ten-fold overdose of sodium benzoate and sodium phenylacetate by intravenous infusion died after experiencing severe metabolic acidosis and circulatory collapse. A patient who received a three-fold overdose of intravenous sodium benzoate and sodium phenylacetate experienced lethargy and vomiting which resolved after the drugs were discontinued. Two patients became irritable and vomited after receiving three-fold overdoses of oral sodium benzoate. Both patients recovered without treatment within 24 hours after the drug was discontinued.

In the event of an overdose of Ucephan, discontinue the drug and institute supportive measures for metabolic acidosis and circulatory collapse.

Hemodialysis or peritoneal dialysis may be beneficial.

Dosage and Administration

For oral use only. Must be diluted before use.

The usual total daily dose for adjunctive therapy of UCE patients is 2.5 mL/kg/day (250 mg sodium benzoate and 250 mg sodium phenylacetate) in three to six equally divided doses. The total daily dose should not exceed 100 mL (10 g each of sodium benzoate and sodium phenylacetate).

Each dose of the drug should be diluted in four to eight ounces of infant formula or milk and administered with meals. If other beverages are used, particularly acidic beverages, precipitation of the drug may occur depending on pH and the final concentration. Therefore, the mixture should be inspected for compatibility before administration.

Ucephan is a concentrated solution and care should be taken in calculating the dose to avoid the possibility of overdosage.

Ucephan is not intended as sole therapy for UCE patients. It should be combined as adjunctive therapy with dietary management (low protein diet) and amino acid supplementation for optimal results.

Because sodium phenylacetate has a lingering odor, care should be taken in mixing and administering the drug to minimize contact with skin and clothing.

How Supplied

Ucephan™ (10% Sodium Benzoate and 10% Sodium Phenylacetate Oral Solution) is supplied in multiple-unit amber glass bottles containing 100 mL of concentrated solution, 6 bottles per case.

NDC

0264-6910-37

Catalog No.

A9100

Fill Vol.

100 mL

Store at room temperature. Avoid excessive heat.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

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Manufactured for:

KENDALL McGAW
LABORATORIES, INC.

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